

## RESEARCH NOTE

## BACTERIOLOGY

## Predominance of Gram-negative bacilli among patients with catheter-related bloodstream infections

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### Abstract

We evaluated changes in the epidemiology of catheter-related bloodstream infections (CRBSIs) between 1996 and 2012 in a tertiary care centre in Israel. The cohort included 1754 episodes of CRBSI. The incidence of CRBSIs decreased throughout the study period, whereas 30-day mortality following bacteraemia increased. There was a linear shift toward predominance of Gram-negative bacilli throughout the study period ( $p$  for trend  $<0.001$ ). In 1996, 68% (68/100) of CRBSIs were caused by Gram-positive cocci, whereas in 2012 77.8% (28/26) were caused by Gram-negative bacilli. The shift towards Gram-negative CRBSIs and the associated mortality mandates that empirical treatment for CRBSIs be directed by local epidemiology.

**Keywords:** *Acinetobacter*, catheter-related bacteraemia, central venous catheter, *Klebsiella*

**Original Submission:** 26 September 2013; **Revised**

**Submission:** 4 December 2013; **Accepted:** 17 January 2014

Editor: E. Tacconelli

**Article published online:** 24 January 2014

*Clin Microbiol Infect* 2014; **20**: O627–O629

10.1111/1469-0691.12565

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### Introduction

Staphylococci are considered the most common pathogens among patients with catheter-related bloodstream infections (CRBSIs). Guidelines recommend empirical glycopeptides

routinely, whereas antibiotics directed against Gram-negative bacilli are recommended more selectively, targeting local epidemiology, critically ill or neutropenic patients. In recent years, the prevalence of Gram-negative organisms among CRBSIs might be increasing, reinforcing the need for their empirical coverage. We evaluated changes in the epidemiology of CRBSI during the period 1996–2012.

We retrospectively included children and adults with CRBSIs between 1996 and 2012 in the Rambam Health Care Campus, Haifa, Israel, a 942-bed primary and tertiary, university-affiliated hospital. The CRBSIs were identified by growth of the same microorganism (type and antibiotic susceptibility) from the catheter tip and from at least one blood culture within 7 days. Throughout the study period, blood cultures were recommended for suspected sepsis and bacteraemia and local hospital guidelines for prevention of CRBSIs existed. An active bundle approach for CRBSI prevention [1] with surveillance and reporting of catheter-associated bloodstream infections was initiated in 2010 in the hospital's intensive care units (ICUs). Silver-sulphadiazine-chlorhexidine-impregnated catheters entered routine use in the adult medical-surgical ICU (18 beds) and paediatric ICU (ten beds) in 2004.

Semi-quantitative catheter tip cultures were performed on sheep blood agar plates (Hy Laboratories Ltd, Rehovot, Israel), using the roll plate method with a cut-off of 15 CFU [2]. Blood cultures were performed using the automated Bac-T-Alert (Biomérieux, Marcy l'Etoile, France) initially and Bactec 9240 (Becton Dickinson, Franklin Lakes, NJ, USA) systems later. Bacterial isolates were identified to the species level using manual biochemical tests and the VITEK-2 system (bioMérieux).

Incidence of CRBSIs was expressed per 1000 hospital-days [3]. Significance was tested using the chi-square  $p$  for trends. The study was approved by the local ethics committee.

The cohort included 1754 episodes of CRBSI caused by 1859 bacteria (105 episodes were polymicrobial); 17.4% of episodes occurred in children (median age 1 year, range 0–18) and 82.6% among adults (mean age 58.4 years, SD 19.4). There was no significant change in patients' age throughout the study years. The incidence of CRBSI episodes per year decreased significantly and linearly throughout the study years ( $p <0.001$  for trend). The incidence was 0.52/1000 hospital-days between 1996 and 2003 versus 0.21/1000 hospital-days between 2004 and 2012.

We observed a gradual shift between 1996 and 2012 toward a predominance of Gram-negative bacilli, ( $p <0.001$ , Fig. 1). In 1996, 68% (68/100) of CRBSIs were caused by Gram-positive cocci, whereas between 2010 and 2012, 76% (94/123) were caused by Gram-negative bacilli. Between 2010 and 2012, *Pseudomonas aeruginosa* was the most common

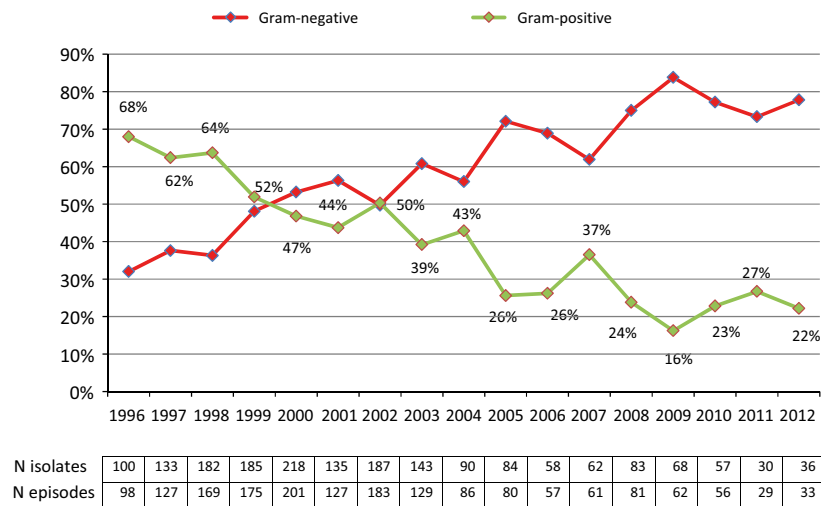


FIG. 1. Percentage of Gram-positive cocci and Gram-negative bacilli per year among CRBSIs.

pathogen (22%), followed by *Klebsiella* sp. (19.5%), *Staphylococcus aureus* (16.3%) and *Acinetobacter* sp. (14.6%) (Table 1). Of the Gram-negatives, 47% (43/92) were resistant to ceftazidime, 39% (31/80) to piperacillin-tazobactam and 24% (22/93) to imipenem. Of the *S. aureus* CRBSIs, 55% (11/20) were methicillin-resistant. Similar trends showing a change from predominance of Gram-positive bacteria to predominance of Gram-negative bacteria were observed in the paediatric and adult subpopulations, when the analysis was limited to the ICU and among haematological cancer patients. The percentage of CRBSIs acquired in the adult and paediatric ICUs decreased from 36.4% (467/1283) between 1996 and 2003 to 22.2% (128/576) after introduction of the impregnated catheters to these ICUs. Thirty-day mortality increased concomitantly with the shift towards Gram-negative bacteria, averaging 6.6% (58/879 patients, only patients' first episode counted) in the first half of the study and 27.2% (97/356 patients) in the second half ( $p < 0.01$  for trend along the years).

TABLE 1. Pathogen distribution among catheter-related bloodstream infections during 2010–2012

	N isolates	Percent
<i>Staphylococcus aureus</i>	20	16.3
<i>Enterococcus</i> sp.	8	6.5
Coagulase-negative staphylococcus	1	0.8
Total Gram-positive	29	24
<i>Acinetobacter</i> sp.	18	14.6
<i>Escherichia coli</i>	4	3.3
<i>Enterobacter</i> sp.	6	4.9
<i>Klebsiella</i> sp.	24	19.5
<i>Proteus</i> sp.	6	4.9
<i>Providencia</i> sp.	4	3.3
<i>Pseudomonas aeruginosa</i>	27	22.0
<i>Serratia</i> sp.	4	3.3
<i>Stenotrophomonas maltophilia</i>	1	0.8
Total Gram-negative	94	76

During a 17-year period the incidence of CRBSIs has dropped significantly and bacteriology has changed from predominance of staphylococci to predominance of Gram-negative bacilli. In the last 3 years, approximately 75% of CRBSIs were caused by Gram-negative bacilli. Concomitantly, 30-day mortality following CRBSIs increased.

In a 700-bed university hospital in Barcelona, Spain, the proportion of Gram-negatives increased from 4.7% in 1991 to 40.2% in 2008 [4]. Another hospital in Barcelona reported a shift towards Gram-negative CRBSIs in their ICU but not in other wards, attributing the change to implementation of a bundled strategy for CRBSI prevention, which preferentially affected Gram-positive CRBSIs [5]. In a large general hospital in Madrid, there was an average annual increase of Gram-negative CRBSIs of 8.9% between 2003 and 2010, whereas the incidence of Gram-positives decreased by 25% [3]. The National Healthcare Safety Network reported on pathogen distribution of central line-associated bloodstream infections in the USA. Between 2006 and 2007, 17.7% of central line-associated bloodstream infections were caused by Gram-negative bacilli, [6] and between 2009 and 2010 this proportion was 25.6% [7]. Hence, a shift towards Gram-negative central catheter infections might be occurring in several locations, although near dominance of Gram-negatives, as in our centre, has not been previously reported.

We included by definition only those CRBSIs in which the catheter was extracted and we did not have information on other sources of infection. However, the same process for CRBSI identification was applied throughout the years, so the data should reflect trends over time. We had no data on central catheter site. Femoral placement predisposes to Gram-negative infections; however, through the years the

use of femoral catheters in our centre declined. No change in the methods of coagulase-negative staphylococci isolation or reporting occurred during these years. Possible explanations for the increase in Gram-negative CRBSIs include a 50% increase in the number of haematological bone marrow transplantations, as well as the number of beds in the hospital ICUs. Silver sulphadiazine-chlorhexidine-impregnated catheters might shift CRBSI epidemiology towards Gram-negative infections, [5] although most CRBSIs throughout the study period occurred outside the ICUs using these catheters. The increase in mortality is probably multifactorial, related mostly to changes in patient case-mix, although the contribution of inappropriate empirical antibiotic treatment [8] and less effective definitive treatment of multidrug-resistant Gram-negative isolates [9] cannot be ruled out. A recent study from Spain showed similar high rates of mortality among patients with *P. aeruginosa* CRBSI, the most common pathogen in our institute [10].

In conclusion, we report a significant shift in the epidemiology of CRBSIs towards a predominance of Gram-negative CRBSIs. The percentage of methicillin-resistant staphylococci out of all CRBSIs was <10%, questioning the need for empirical vancomycin for suspected CRBSIs in our setting. Conversely, Gram-negative CRBSIs are associated with significant mortality and empirical treatment must address their increasing prevalence. Empirical treatment of CRBSIs should be directed by local epidemiology.

## Funding

None.

## Conflicts of Interests

All authors have declared that they have no conflicts of interest.

## Transparency Declaration

The authors declare no conflicts of interest.

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